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**Heightened impulsivity: associated with family history of alcohol misuse, and a  
consequence of alcohol intake**

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## 33 Abstract

34 **Background:** Youths with Family History of alcoholism are at greater risk of developing Alcohol  
35 Use Disorder (AUD); heightened impulsive behaviour may underlie such increased  
36 vulnerability. Here we studied waiting impulsivity (previously suggested to predispose to  
37 alcohol drinking) in young moderate-to-heavy social drinkers (18-33 years old) characterised  
38 as family history-positive (FHP) and -negative (FHN) following an alcoholic or non-alcoholic  
39 (placebo) drink. **Methods:** Two groups of young male and female social drinkers (n=64) were  
40 administered an acute dose of alcohol (0.8g/kg) or placebo. One group (FHP; n= 24) had first-  
41 degree relatives with problems of alcohol misuse; the other group did not (FHN). Participants  
42 completed four variants of the Five-Choice Serial Reaction Time task, a task measuring waiting  
43 impulsivity. In addition, other types of impulsive behaviour were tested (by means of the Stop  
44 Signal Reaction Time, SST; Information Sampling Task, IST; Delay Discounting Questionnaire,  
45 DDQ, Two-Choice Impulsivity Paradigm, TCIP; and Time Estimation, TET). **Results:** Young FHP  
46 adults showed more premature responding than FHN when evaluated under increased  
47 attentional load (high waiting impulsivity), whilst, in contrast, they presented a more  
48 conservative strategy on the IST (less impulsive behaviour), compared to FHN. Acute alcohol  
49 impaired inhibitory control on the SST in all participants, and induced a marginal increase of  
50 premature responses, but did not affect other measures of impulsivity. **Conclusions:** Assessing  
51 for exaggerated waiting impulsivity may provide a potential endophenotype associated with  
52 risk for the development of alcohol addiction (i.e. offspring of alcoholics).

53 **Key Words:** impulsivity, family history of alcoholism, alcohol, binge drinking, social drinkers.

## 54 INTRODUCTION

55 Impulsivity, a predisposition towards risky and premature responding, is potentially a  
56 maladaptive trait influencing excessive alcohol drinking and leading to alcohol use disorder  
57 (AUD). Different forms of impulsive behaviour are recognised (Evenden, 1999), which depend  
58 on different neural networks (Dalley et al., 2011). In the current report, we concentrate on  
59 “waiting” impulsivity, characterized in both rodents (Robbins, 2002, Sanchez-Roige et al.,  
60 2012) and humans (Voon, 2014, Sanchez-Roige et al., 2014a), as a tendency to premature  
61 responding in a reward-related task. Mouse strains predisposed to excessive alcohol  
62 consumption (compared to strains which are not) show heightened waiting impulsivity in the  
63 5-choice serial reaction time task (5CSRTT) (Sanchez-Roige et al., 2014a). These findings lead  
64 to the suggestion that waiting impulsivity may predispose to poor control over alcohol  
65 drinking. In rodent models, exaggerated waiting impulsivity may also result from acute alcohol  
66 ingestion, or following long-term alcohol exposure: both acute doses of ethanol (Sanchez-  
67 Roige et al., 2014b, Oliver et al., 2009) and exposure of adolescent mice to binge-patterns of  
68 alcohol lead to increased impulsivity (Sanchez-Roige et al., 2014b).

69 Links between heightened impulsivity and excessive alcohol use have also been established in  
70 humans. However, with no comparable methods between the species for characterising  
71 impulsivity, it is unclear that data obtained from animals correspond to aspects of impulsivity  
72 of relevance to human alcohol abuse. The use of a human homologue of the mouse 5CSRTT  
73 (Sx-5CSRTT) has shown that among heavy social alcohol drinkers, binge-drinkers (compared  
74 to non-binge drinkers) are impaired in the human version of a task (Sanchez-Roige et al.,  
75 2014a). We now extend the mouse-human comparison to explore the effects of acute alcohol

on waiting impulsivity in humans at risk for alcohol misuse (FHP vs. FHN), with the aim of further understanding the role of “waiting” impulsivity in predisposing to AUD.

Positive family history is a consistent risk factor for AUD (for a review: Schuckit 2009), with heritability estimates ranging from 45-65%. FHP individuals are likely to initiate alcohol use earlier, and are at greater risk for AUD (e.g. Lieb et al., 2002). It is hypothesized that heightened individual risk for AUD, both familial and non-familial, may be mediated by impulsivity (Sher et al., 1991).

Impulsivity deficits may hence be present prior to initiation of alcohol abuse. Evidence from prospective studies shows that pre-existing levels of high-impulsivity in childhood are associated with early alcohol use, and alcohol misuse (Kirisci et al., 2006). Moreover, compared to FHN youth, the offspring of alcoholics tend to show greater impulsive behaviour: they are more likely to make impulsive errors, and show decision-making biases (for a review see: Salvatore et al., 2015). Behavioural deficits in FHP are associated with disruptions in frontostriatal circuitry (reviewed by Cservenka, 2015), systems necessary for efficient inhibitory control. Premorbid behavioural (impulsive) phenotypes in FHP youth may contribute to the heritable aspects of AUD.

We were therefore interested to study whether familial influences on alcoholism may be mediated by impulsivity traits. We addressed this question by assessing a number of impulsivity forms in individuals with and without a family history of alcoholism. If FHP individuals show higher impulsivity, even if they have not themselves developed alcohol problems, this may indicate premorbid behavioural phenotypes in FHP youth (‘impulsive endophenotype’) (Gottesman and Gould, 2003) associated with vulnerability to future alcoholism (Sher et al., 1991). Some forms of impulsivity have already been proposed as a behavioural endophenotype (produced reliable genetic associations; e.g. increased in siblings

of drug abusers) mediating risk for other substance use disorders (stimulants), which may be exacerbated by chronic drug exposure (Ersche et al., 2012). Data indicating that impulsivity is highly heritable (e.g. VanderBroek et al., 2015) lends further support to the idea of impulsivity as an intermediate phenotype for AUD (Peña-Oliver et al., 2016). However, the role of waiting impulsivity as a premorbid factor for alcohol abuse, and its modification by acute alcohol in the absence of AUD, remain unexplored.

As in the mouse, alcohol can trigger and exacerbate impulsive tendencies in humans (e.g. Marcinski et al., 2005, Loeber and Duka, 2009), with decreased activity in frontal regions explaining the alcohol-induced deficits (e.g. Nikolaou et al., 2013). Here we examined impulsivity changes in individuals at risk for AUD (FHP), in the presence or absence of acute binge alcohol exposure, compared to individuals not at familial risk (FHN).

To this aim, two groups, FHP and FHN young social drinkers participated in a single session where they received 0.8g/kg of alcohol, or placebo, before performing the Sx-5CSRTT, to assess anticipatory behaviour (premature responding), a measure of waiting impulsivity. Participants were also characterized in four additional measures of impulsivity, based on different operational definitions of the construct (Caswell et al., 2015). The Stop Signal Task, used to assess ability to inhibit a prepotent response (“can’t stop”) (Logan, 1994), served as an additional measure of ‘motor impulsivity’ (Dalley et al., 2011). Reflection Impulsivity (inadequate information sampled before executing a response) was measured by the Information Sampling Task (IST; Clark et al., 2006), and temporal impulsivity (preference for immediate small over delayed large rewards) was measured by the Delay Discounting Questionnaire (DDQ) (Richards et al., 1999) and the Two Choice Impulsivity paradigm (TCI) (Dougherty et al., 2005). Finally, the Time Estimation Task (TET) was used to establish

relationships between impulsive behavioural tendencies and time perception. Impulsive personality traits of participants were evaluated by the Barratt Impulsivity scale (BIS).

Based on our previous findings (Sanchez-Roige et al., 2014a) we predicted familial risk for AUD would be reflected in increased “waiting” impulsivity, suggesting a potential endophenotype. We further predicted increased impulsive responding after acute doses of alcohol; compared to FHN subjects, we anticipated elevated impulsive responding in FHP subjects in the context of alcohol.

## **MATERIAL AND METHODS**

### **Recruitment and Procedure**

64 participants (30 male; age 18-35 years,  $M = 21.98$ ,  $SD = 3.22$ ) were recruited from the University of Sussex subject pool. Participants were assigned to FHP (24 participants) or FHN groups using scores from the Family Tree Questionnaire (Mann et al., 1985). Alcohol drinking patterns were calculated based on the Alcohol Use Questionnaire (Mehrabian and Russell, 1978): all participants were healthy moderate-to-heavy social drinkers (see Supplementary Material for further details of inclusion criteria), drinking 10-60 units of alcohol per week (one unit = 8 g of alcohol in UK). Participants were required not to be heavy smokers (<10 cigarettes/day): 18.3% had never smoked cigarettes, 11% were occasional smokers (1-5/day), 8% were moderate smokers (4-10/day); 68.8% had never used illicit recreational drugs, 26.6% indicated occasional use of cannabis (less than once per week).

Upon arrival at the laboratory, subjects were breathalysed (Lion Alcolmeter SD-400; Lion Laboratories, Barry, UK) to ensure zero breath alcohol levels (%BACw/v; BAC). Participants then completed:

- 146 a) *Personal Details Questionnaire* (age, date of birth, smoking status, current medication);
- 147 b) *Barratt Impulsiveness Scale*, version 11 (BIS-11; Patton et al 1995), a 30-item checklist that  
148 gives a total impulsivity score and three sub-scores of attentional, motor, and non-planning  
149 impulsiveness;
- 150 c) *Alcohol Use Questionnaire* (Mehrabian and Russell, 1978), *Alcohol Use Disorder*  
151 *Identification Test* (AUDIT; Saunders et al 1993), and Structured Interview Questionnaire  
152 (Duka et al. 2002, interview adapted for social drinkers: see Supplementary), to evaluate heavy  
153 drinking and/or active alcohol abuse or dependence;
- 154 d) *Drug Use Questionnaire* (Townshend and Duka, 2005), which provides information on  
155 duration of use, time since last use, and how often used for all the main drug categories. On  
156 the basis of the later, a drug use pattern is evaluated as follows: “no drug use”, “occasional  
157 cannabis use”, “regular cannabis use” (at least once a week), and “recent use of more than  
158 one type of illegal drug”.
- 159 e) *Family History Assessment*: Positive score: one or more first-degree relatives with alcohol-  
160 misuse history (as per Family Tree Questionnaire [Mann et al. 1985]; see Supplementary for  
161 further details);
- 162 f) *Beck Depression Inventory II* (BDI; Beck et al., 1996), a 21-item multiple choice checklist  
163 measuring severity of depression;
- 164 f) *Rey Auditory Verbal Learning Test* (RAVLT, Rey, A. (1941), list of 15 items that the participant  
165 must remember and recall, to measure short-term memory capacity;



and g) *Alcohol visual analogue scale* (VAS; Duka et al., 1998), a set of 90mm visual analogue scales to measure how much a mood state (contented, lightheaded and relaxed) applies to participants at that moment.

Prior to drink consumption, the participant's body weight/height was recorded, and the Body Mass Index ( $BMI = (\text{weight}[\text{lb}]/\text{height}^2[\text{in}]) * 703$ ) was calculated. Participants were administered a 0.8g/kg alcohol dose or placebo, according to a between-subjects randomized double-blind placebo-controlled design (see Loeber and Duka, 2009, for details). After a 10-minute break (post-drink), a further BAC was recorded and participants completed the VAS. Following instruction and practice trials, participants were presented with six computerised tasks (see below; Sx-5CSRTT, SST, IST, TCIP – random order; DDQ and TET - at the end of the experiment). At the end of the session (90 minutes), participants were again breathalysed, and completed the VAS. Participants were then informed of their breath alcohol levels and were required to remain in the laboratory until their BAC fell to below half the UK legal driving limit ( .17 %BAC w/v). All participants gave informed consent to take part in the study, which was approved by the University of Sussex ethics committee. Participants were paid £15 (£2 for each additional hour).

### **Behavioural Measures of Impulsivity**

The Sussex Five Choice Serial Reaction Time Task (Sx-5CSRTT) was administered using an iPad (iOS 8 operating system; Apple Inc; see Sanchez-Roige, 2014a for a detailed description). Participants were required to detect and respond to the brief (0.5s) highlighting of one of five moving visual stimuli. Responding before stimulus onset was considered a measure of poor inhibitory control, recorded as a premature response and followed by a 5s time-out period.

Following practice trials in which the stimulus was presented every 5s (ITI 5-s) participants performed four task variants: a fixed (fITI) and a variable (vITI) session under simple task conditions; and, in order to increase the attentional load, a fITI and vITI session in combination with a dual task (Hogarth et al., 2008) in which subjects were also required to respond to a 659 Hz tone by performing a key press with the non-dominant hand. Main outcome variables were ‘percentage of premature responding’ and ‘total number of premature responses’.

The Stop Signal task (SST; Logan, 1994) to test response inhibition; the Information Sampling Task (IST; Clark et al., 2006), to evaluate ‘reflection’ impulsivity by measuring how much information participant’s gather prior making a decision; a delay discounting questionnaire (DDQ; Richards et al., 1999); and Two Choice Impulsivity paradigm (TCIP; Dougherty et al., 2005), to assess preference for a small immediate over a large delayed reward; and the Time Estimation Task (TET) to evaluate the subject’s time perception were added. Main outcome variables included the calculated Stop Signal Reaction Time (‘SSRTi’) from SST; ‘number of boxes opened’ and ‘number of errors’ (fixed- and decreased-win conditions) from IST; the discounting curve ( $k$  parameter) from DDQ, and ‘proportion of immediate choices’ from the TCIP; and the subject’s ‘accuracy of performance’ in TET. See Supplementary material for details of the tasks and analysis of main variables.

## **Statistical analysis**

Statistical analyses were performed using the “Statistical Package for Social Sciences” (SPSS, version 20.0). Baseline demographics and trait measurements were analysed with independent  $t$  tests. Breath alcohol concentrations (BAC) were analysed pre- cognitive tasks using univariate analysis; gender was subsequently included as a factor, to check that male and female BACs did not differ. Repeated measures ANOVA was used to compare BAC levels

and VAS scores across time (pre-, post- drink) as within-subject factors and FH and alcohol condition as between factors.

Following three-way ANOVA with FH (2 levels: FHP, FHN), alcohol condition (2 levels: alcohol, placebo) and gender (2 levels) as between factors, the effects of FH and alcohol dose on impulsivity were explored using a two-way ANOVA (as there were no gender differences, this factor was excluded from the analysis). Two-way analyses of covariance were run with both 'Binge Drinking Score' and 'Age' as covariates, as they represent important factors associated with impulsivity (e.g. Smith et al., 2015). In addition, a separate two-way analysis of covariance was run with 'Total-BIS', to ensure that the group differences in self-reported BIS were not influencing behavioural measures of impulsivity (see Supplementary). 'BIS-attentional subscale', 'AUDIT' scores were square-root transformed, 'Binge score', 'AUQ', 'k', 'BDI', 'boxes opened' (fixed win), 'percentage of premature responses' (4 sessions) were log<sub>10</sub> transformed, and 'time estimation accuracy' was arcsine transformed [ $x' = 2\arcsine(\sqrt{x/100})$ ] to obtain homogeneity of variance (Levene's test), though untransformed means are shown throughout. If the assumptions of normality were violated, non-parametric statistics were used: 'age', 'Daily cigarette use', 'RAVLT', items from the semi-structured interview and from the Drug Use Questionnaire were analysed by Mann-Whitney *U* tests. Significance was set at  $\alpha=0.05$ . Effect sizes are reported using eta values ( $\eta^2$ ) or *r*.

## RESULTS

### ***Baseline group demographics, trait measurements and drug use patterns***

Participants were randomly allocated to the alcohol or placebo groups. The four groups were matched for age, gender and short-term memory capacity (see Table 1). Patterns of drinking

(units/week, binge scores, AUQ scores; AUDIT scores;  $F < 0.498$ ,  $ps > .05$ ,  $\eta^2 < .008$ ) or drug use (cannabis, other illegal drugs;  $U(64) < 368.50$ ,  $ps > .05$ ,  $r = 0.21$ ) were similar between groups. However, participants in the placebo group showed higher self-reported impulsiveness (total-BIS;  $F(1,63) = 6.980$ ,  $p = .011$ ,  $\eta^2 = .101$ ) than subjects in the alcohol group. Group characteristics for the FHP and FHN groups are given in Table S1. Groups were matched for age, gender and short-term memory capacity (RAVLT). FHP subjects did not differ from FHN in measures of self-reported BIS-impulsivity, BDI scores, alcohol drinking patterns or AUDIT scores ( $t(62) < 0.519$ ,  $ps > .05$ ,  $d = .12$ ,  $r = .06$ ). However, in a structured interview 43.5% of FHP subjects reported occasionally feeling guilty after drinking (vs. 10.3% in FHN groups;  $U(62) = 310.0$ ,  $p = .010$ ,  $r = 0.33$ ), and 21.7% drink to get high (vs. 5.1%, FHN;  $U(62) = 374.0$ ,  $p = .048$ ,  $r = 0.25$ ); 43.5% reported a tendency to occasionally drink without breaks (vs. 23.1%, FHN;  $U(62) = 357.0$ ,  $p = .095$ ,  $r = 0.21$ ).

### ***Breath alcohol levels***

As expected, BAC levels prior to testing in the cognitive tasks differed across alcohol conditions (alcohol:  $F(1,59) = 345.080$ ,  $p = .001$ ,  $\eta^2 = .787$ ; Table 1). Following task completion, BAC levels were lower (time:  $F(1,59) = 5.639$ ,  $p = .021$ ,  $\eta^2 = .080$ ); and again, as anticipated, differed across treatment groups (alcohol:  $F(1,59) = 738.870$ ,  $p = .001$ ,  $\eta^2 = .923$ ). No other effects or interactions were found ( $F < 0.123$ ,  $ps > .05$ ,  $\eta^2 < .001$ ).

### ***FHP's performance on The Sussex-Five Choice Serial Reaction Time Task***

Sx-5CSRTT performance of FHP and FHN subjects, with matching alcohol and placebo groups, is illustrated in Fig. 1.

When the task was performed under single task conditions, no FH differences were found on premature responding, either during the fITI or vITI sessions (FH:  $F_s < 0.130$ ,  $p_s > .05$ ,  $\eta^2 < .002$ ; with 'Binge Drinking' plus 'Age' included as covariates:  $F_s < 0.150$ ,  $p_s > .05$ ,  $\eta^2 < .003$ ; Fig. 1A). Alcohol ingestion showed a tendency to increase premature responding during the first fITI session (alcohol:  $F(1,58) = 3.675$ ,  $p = .06$ ,  $\eta^2 = .063$ ; Binge Drinking/Age:  $F(1,58) = 3.300$ ,  $p = .075$ ,  $\eta^2 = .056$ ), but not the second vITI session (alcohol:  $F(1,58) = 1.129$ ,  $p = .293$ ,  $\eta^2 = .020$ ; Binge Drinking/Age:  $F(1,58) = .439$ ,  $p = .510$ ,  $\eta^2 = .007$ ).

When the task was performed under dual task conditions, again, no effects of FH or alcohol ingestion were detected for premature responding during the fITI session (FH or alcohol:  $F_s < 1.293$ ,  $p_s > .05$ ,  $\eta^2 = .023$ ; Binge Drinking/Age:  $F_s < 1.349$ ,  $p_s > .05$ ,  $\eta^2 < .023$ ; Fig. 1B). However, FH group differences emerged during the vITI-dual task session: FHP subjects showing a high percentage of premature responses (FH:  $F(1,58) = 4.291$ ,  $p = .043$ ,  $\eta^2 = .067$ ; Binge Drinking/Age:  $F(1, 58) = 5.298$ ,  $p = .025$ ,  $\eta^2 = .078$ ; Fig. 1B). Although alcohol did not increase premature responding in the vITI-dual task session (alcohol:  $F(1,58) = 1.310$ ,  $p = .257$ ,  $\eta^2 = .023$ ; Binge Drinking/Age:  $F(1,58) = 0.986$ ,  $p = .325$ ,  $\eta^2 = .015$ ; Fig. 1B), alcohol ingestion marginally increased the total number of premature responses across the four sessions (alcohol:  $F(1,58) = 3.761$ ,  $p = .058$ ,  $\eta^2 = .063$ ; Binge Drinking/Age:  $F(1, 58) = 2.929$ ,  $p = .093$ ,  $\eta^2 = .048$ ; Table 3). For any of the challenges, no FH by alcohol interactions appeared in the analysis ( $F(1,58) = 2.232$ ,  $p = .141$ ;  $\eta^2 = .035$ ; Binge Drinking/Age:  $F(1,58) = 2.063$ ,  $p = .157$ ,  $\eta^2 = .031$ ).

Both FH groups performed the dual task similarly (FH:  $F < 0.430$ ,  $p_s > .05$ ,  $\eta^2 = .006$ ; Table 3), but alcohol ingestion decreased accuracy in detecting high tones (alcohol: fITI,  $F(1,59) = 16.840$ ,  $p = .001$ ,  $\eta^2 = .228$ ; vITI,  $F(1,59) = 19.839$ ,  $p = .001$ ,  $\eta^2 = .260$ ), with a tendency to be more acute in FHP participants (FH x alcohol: fITI:  $F(1,59) = 3.021$ ,  $p = .088$ ,  $\eta^2 = .041$ ).

### ***FHP's performance on additional behavioural measures of Impulsivity***

There were no FH differences during the SST task (FH:  $F(1,59) = 0.742, p = .393, \eta^2 = .010$ ; Binge Drinking/Age:  $F(1,58) = 0.747, p = .391, \eta^2 = .022$ ; Fig. 2), but alcohol increased SSRTi (alcohol:  $F(1,59) = 15.193, p = .001, \eta^2 = .209$ ; Binge Drinking/Age:  $F(1,58) = 13.652, p = .001, \eta^2 = .188$ ). In contrast, an effect of FH emerged in the IST, or 'reflection' impulsivity: compared to FHN, FHP subjects opened more boxes and made fewer errors (FH:  $F(1,63) = 6.896, p = .011, \eta^2 = .101$ ,  $F(1,63) = 5.590, p = .021, \eta^2 = .080$ , respectively; Binge Drinking/Age:  $F(1,58) = 6.751, p = .012, \eta^2 = .086$ ;  $F(1,58) = 7.121, p = .010, \eta^2 = .093$ ) when the amount of win was fixed (Fig. 3A-B). Under a decreased-win condition, FH groups performed similarly (FH:  $F_s < 3.547, p_s > .05, \eta^2 = .054$ ; Binge Drinking/Age:  $F_s < 3.267, p_s > .05, \eta^2 < .043$ ; Fig. 3C-D). With regards to DDQ 'temporal' impulsivity, FH effects did not appear: all groups showed a similar linear decrease of indifference point as a function of increased delay (although a tendency for lower impulsivity was observed in FHP participants:  $F(1, 61) = 3.085, p = .084, \eta^2 = .048$ ; Binge Drinking/Age:  $F(1, 61) = 2.913, p = .093, \eta^2 = .047$ ; see Table 4 for  $k$  values,  $R^2$  values  $> 0.97$ ). In addition, no effects of FH were detected on the accuracy of time estimation (FH:  $F(1, 62) = 0.293, p = .590, \eta^2 = .005$ ; Binge Drinking/Age:  $F(1, 61) = .391, p = .619, \eta^2 = .004$ ; Table 3). Alcohol did not disrupt performance in any of these tasks (alcohol: DDQ, IST, DDQ, TCIP, TET;  $F_s < 2.124, p_s > .05, \eta^2 < .030$ ; Binge Drinking/Age:  $F_s < 1.441, p_s > .05, \eta^2 < .019$ ), and other FH or alcohol by FH interactions were not detected ( $F < 2.096, p_s > .05, \eta^2 < .032$ ; Binge Drinking/Age:  $F_s < 2.530, p_s > .05, \eta^2 < .034$ ).

### ***Mood changes***

There were no significant baseline (pre-drink) group differences in VAS mood ratings (FH or alcohol effects:  $F < 2.116, p_s > .05$ ). Following the drinking protocol, lightheaded ratings

changed (time:  $F(1,60)= 68.948, p= .001, \eta^2= .432$ ; see Table 2), and a significant time by alcohol condition interaction emerged ( $F(1,60)= 27.983, p= .001, \eta^2= .176$ ); lightheaded scores post- drink were higher in all participants compared to pre- drink ratings, and participants in the alcohol condition feeling more lightheaded than those in the placebo group. Ratings of relaxedness did not vary over time (time:  $F(1,60)= 1.383, p= .244, \eta^2= .020$ ), but a time by FH interaction revealed decreased relaxedness in FHP participants (Time x FH:  $F(1,60)= 5.443, p= .023, \eta^2= .079$ ). At the end of the drinking protocol, all participants were feeling more contented (time:  $F(1,60)= 5.276, p= .025, \eta^2= .076$ ; yet this effect was less apparent for FHP in the placebo condition, revealed by a marginal time by FH interaction:  $F(1,60)= 2.963, p= .090, \eta^2= .042$ ).

## DISCUSSION

We set out to examine waiting impulsivity using the 5-CSRTT in young FHP adults in comparison to FHN individuals, following alcohol or placebo treatment. We also extend our observations to other types of impulsivity using a battery of impulsivity tasks. We found greater waiting impulsivity in FHP individuals when performing the task under a vITI in parallel with the dual task, irrespective of alcohol intoxication, suggesting a pre-existing vulnerability factor. Contrary to our expectation, we did not find evidence of increased impulsivity in FHP subjects following acute alcohol ingestion, although we did observe greater attentional impairments (a tendency for more omission errors [see Supplementary], and impaired high-tone detection in the Sx-5CSRTT) compared to FHN. Unexpectedly, FHP participants displayed a more cautious strategy during the IST revealing a dissociation of FH-effects. Personality traits of impulsivity were similar in FH groups. Although the groups did not differ in their alcohol drinking history, FHP reported more “drinking to get intoxicated”, and “feelings of guilt”

following consumption. Moreover, we found that alcohol exposure elevated impulsive behaviour (inability to wait, or cancel a response), but, in contrast, did not affect reflection or choice impulsivity.

#### **FHP and ‘motor’ impulsivity: heightened ‘waiting’ impulsivity under challenging conditions**

Heightened waiting impulsivity is a robust predictor of high drug taking in animal models (Dalley et al., 2011). The introduction of parallel tests in rodents and humans showing that premature responding was enhanced both in alcohol-naïve, high ethanol-consuming mouse strains, and human binge drinkers (Sanchez-Roige et al., 2014a) suggests that this may also be true for humans. We extended those findings by demonstrating here elevated ‘waiting’ impulsivity in FHP, suggesting further that reduced ability to wait may contribute to a pre-existing vulnerability for high alcohol drinking. Recent data showing waiting impulsivity to be impaired in binge drinkers and AUD individuals compared to control (Morris et al., 2015) further supports our hypothesis. The finding that premature responding was associated with lower connectivity in regions of the frontostriatal circuitry (Morris et al., 2015), regions also implicated from rodent lesion studies (Dalley et al., 2011), indicates that the behavioural deficit observed in FHP may be coupled with reduced function in frontostriatal networks. Together, behavioural and neural correlates of premature responding may be endophenotypic markers of AUD (Salvatore et al., 2015).

In another form of impulsive behaviour, impulsivity occurs as a failure to cancel actions when a ‘stop’ signal is presented. Action cancellation in a SST task has been proposed as a ‘SSRT endophenotype’ for stimulant dependence (Ersche et al., 2012). In the present study, SSRT was not greater in FHP individuals. This finding confirms that impulsivity subtypes (waiting,



stopping) may occur independently of one another (Caswell et al., 2015), in keeping with them being governed by distinct neural networks (Morris et al., 2015).

#### **Double dissociation of FH backgrounds on motor vs. reflection/choice impulsivity**

The inability to weigh evidence, or ‘reflection’ impulsivity, is also critical to behavioural regulation. Binge drinkers (Townshend et al., 2014) and AUD participants (in abstinence) (Lawrence et al., 2009) have previously been shown to make decisions at higher levels of uncertainty, with a greater number of errors. And yet, in the current study, FHP individuals accumulated more evidence (opened more boxes) before making a decision, thus making fewer errors. This finding was unexpected; it suggests that FHP participants tolerated a smaller degree of uncertainty, and were more cautious in integrating the information gathered. Some participants in the present study (both FHP and FHN), although classified as moderate-to-heavy binge drinkers (Sanchez-Roige et al., 2014a), may be considered as heavy drinkers and potentially suffering from AUD, though no formal diagnosis was made; therefore, it seems possible that their heightened reflection impulsivity results from alcohol abuse, while FHP individuals may be more prone to greater risk aversion, as previously suggested (Banca et al., 2015).

Concerning the delayed discounting measures in which reward is devalued as a function of time, the findings are unclear. We (Sanchez-Roige et al. 2014a), and others (Banca et al., 2015), did not find differences in binge drinkers; nor was performance in this measure predictive of high alcohol drinking (Whelan et al., 2014). In FH related studies, the literature presents mixed results, but FHP individuals generally display biases towards immediate gratification (Dougherty et al., 2014, Smith et al., 2015). DD may thus be an intermediate phenotype for AUD, with a heritable component (VanderBroek et al., 2015).

In the present study, however, FHP, were marginally less prone to choose immediate rewards. Slower discounting may be accounted for by factors other than impulsivity, such as decreased sensitivity to rewards or risk aversion. However the effect was marginal. Other studies have failed to find differences in delay discounting (e.g. Herting et al., 2010, Petry et al., 2002). We suggest that the inconsistent findings in DDQ in FHP may be related to differences in the groups of participants (adolescence (Dougherty et al., 2015, Smith et al., 2015) vs. young adults) or in methods used to classify FH (well-characterised sample (Dougherty et al., 2014) vs. self-reports). We further extended DDQ findings to TCIP performance, since both measures fall within the domains of ‘choice’ impulsivity, but TCIP uses real-time rather than imaginary delays. FHP did not differ from FHN subjects in this task, consistent with other reports (Acheson et al., 2011).

#### **Acute ethanol effects**

The present study confirmed previous data that alcohol reduces the ability to cancel pre-potent actions in humans (e.g. Caswell et al., 2013, Loeber and Duka, 2009). Regarding waiting impulsivity, in mice, ethanol administration increased premature responding in the 5-CSRTT (Sanchez-Roige et al., 2014b, Oliver et al., 2009). Here alcohol also increased the total number of premature responses in all participants, but this effect was marginal (potentially as a result of our relatively low sample size). Alcohol disrupted attentional performance, increasing the percentage of omitted trials, as observed in mice (Sanchez-Roige et al., 2014b). Those effects may result from a general reduction in the vigour of responding, or sedation under ethanol, consistent with the increased time to make a response and the decreases in speed to collect the points (see Supplementary). We did observe, however, enhanced Sx5CSRTT omissions in intoxicated FHP subjects (see

Supplementary), suggesting that FHP are more vulnerable to the alcohol-induced attentional deficits, consistent with reduced electrophysiological responses to unexpected stimuli (Salvatore et al., 2015). Such an effect of alcohol may contribute in FHP to drinking without attending to cues in the environment that signal the need to stop drinking further.

With regards to ‘reflection’ impulsivity, alcohol ingestion did not alter performance on the IST task. This observation appears at first sight to be inconsistent with findings showing that alcohol impaired performance in a planning task (Weissenborn and Duka, 2003), or increased difficulty in error-monitoring during naturalistic conditions (real money in a gambling task) (Lyvers et al., 2015). However, IST does not challenge problem-solving in the same manner as the above-mentioned tasks, and may be a truer measure of reflection impulsivity (information gathering before a response).

There was no main effect of alcohol on DD, in line with several other studies (Caswell et al., 2013, Dougherty et al., 2008, Richards et al., 1999). It is possible that DD may be impaired only at high BACs (Ortner et al., 2003), since in the current study, participants were on the descending curve of BAC at time of testing; or due to the use of hypothetical delays (ethanol generally impairs DD in rodents, where real-time delays are used (e.g. Olmstead et al., 2006). However, there were also no effects of alcohol on TCIP, where the delays in reward delivery are not hypothetical. Collectively, the effects of alcohol on impulsivity are dissociable (‘motor’ but less solid evidence for ‘reflection’ or ‘choice’ impulsivity).

The lack of a greater effect of acute alcohol on impulsivity measures in FHP individuals may be contrasted with our previous report that a (small) 0.5g/kg alcohol dose induced premature responding to a greater extent in high-impulsive, ethanol preferring mice (vs. low impulsive, non-ethanol preferring mice (Sanchez-Roige et al., 2014b), suggesting that familial predisposition to alcoholism does not correspond in a simple fashion to mouse genetic

models. Regarding SST ('motor' impulsivity subtype), alcohol did not induce greater impairments in FHP subjects, although others have shown less impairment in FHP than FHN subjects (Kareken et al., 2013). Similarly, measures of reflection or choice impulsivity were not affected by alcohol and FH, suggesting that impulsivity deficits in FHP subjects may (more likely) be premorbid, and not merely a consequence of alcohol abuse.

Individuals vary widely in their subjective experience (stimulant, sedative) of the pharmacological and neurobehavioral effects of alcohol. When they were assessed at the end of testing, FHP individuals in the alcohol condition experienced reduced relaxation relative to FHN, similar to previous reports indicating fewer sedative effects as BAC level declines (Ray et al., 2010). This is important, as less sedation may elevate future alcohol consumption (King et al., 2014).

We recognize study limitations. The role of premorbid impulsivity as a predictor of high alcohol drinking cannot be easily disentangled from the consequences of drinking history, as impulsivity measures are almost inevitably assessed after a period of alcohol use. However, in our sample participants were all moderate-to-heavy-alcohol social drinkers, with FHP and FHN reporting drinking similar quantities of alcohol. Moreover, we demonstrated that the prevalence of high impulsivity in FHP subjects was still observed after controlling for the potential effects of 'binge drinking scores' and 'age' (possibly associated with extended alcohol use). Secondly, FH assessment relies on self-report data, which are susceptible to retrospective biases. For instance, participants might be unaware of parental AUD (particularly if their parents recovered before the participants were aware of their condition). Future research may benefit from more fully structured diagnostic interviews. Additionally, FHP group required alcohol-related problems in at least one biological parent or sibling, which may have resulted in heterogeneous FH backgrounds; on the other hand, mothers were not

excluded, possibly allowing individuals with fetal alcohol exposure to be included in the group. Lastly, as a consequence of randomisation, alcohol/placebo groups were not well matched with regard to BIS-impulsivity trait (subjects in the placebo group scored higher). However, these baseline differences do not seem to explain the alcohol-induced effects (covariate analysis). Nonetheless, using a within-group design in future studies may reduce variance and clarify the effects of acute alcohol.

### **Clinical implications and concluding remarks**

FHP individuals exhibited a different pattern of impulsive behaviour from FHN; FHP showed greater waiting impulsivity, but less reflection impulsivity. Impaired performance in waiting impulsivity may offer a measure of impulsivity that represents a premorbid risk factor for heavy drinking (Voon, 2014; and the present report), and one that may be modified by acute alcohol intake. Importantly acute alcohol induced attentional deficits (increase in omissions) in FHP individuals, possibly facilitating deficits leading to alcohol abuse. Deficits in ‘stopping’ are evident following acute doses of alcohol, but its role as a premorbid factor is less clear. That our findings were not consistent across impulsivity subclasses (and that the measures were not correlated [Supplementary]) may suggest that different types of impulsivity contribute to different aspects of alcohol misuse and indicate the importance of employing a broad range of impulsivity measures rather than a single test. Disentangling the biology of high waiting impulsivity (‘endophenotype’) may increase the power to detect the biological factors underlying the risk for AUD.

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476

477 **CONFLICT OF INTEREST**

478 The authors declare no conflicts of interest.

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## FIGURE LEGENDS

**Fig. 1.** Five-Choice Serial reaction time task performance (mean  $\pm$  SEM) by family history status (FH) and alcohol; 'waiting' impulsivity levels during the simple task (**A**) and in combination with the dual task (**B**). Alcohol ingestion marginally increased premature responses during the first challenge ( $p = .058$ ; **A**). Under the vITI dual condition, FHP participants had more premature responses than FHN ( $p = .043$ ; **B**), suggesting greater waiting impulsivity, irrespective of the acute effects of alcohol.

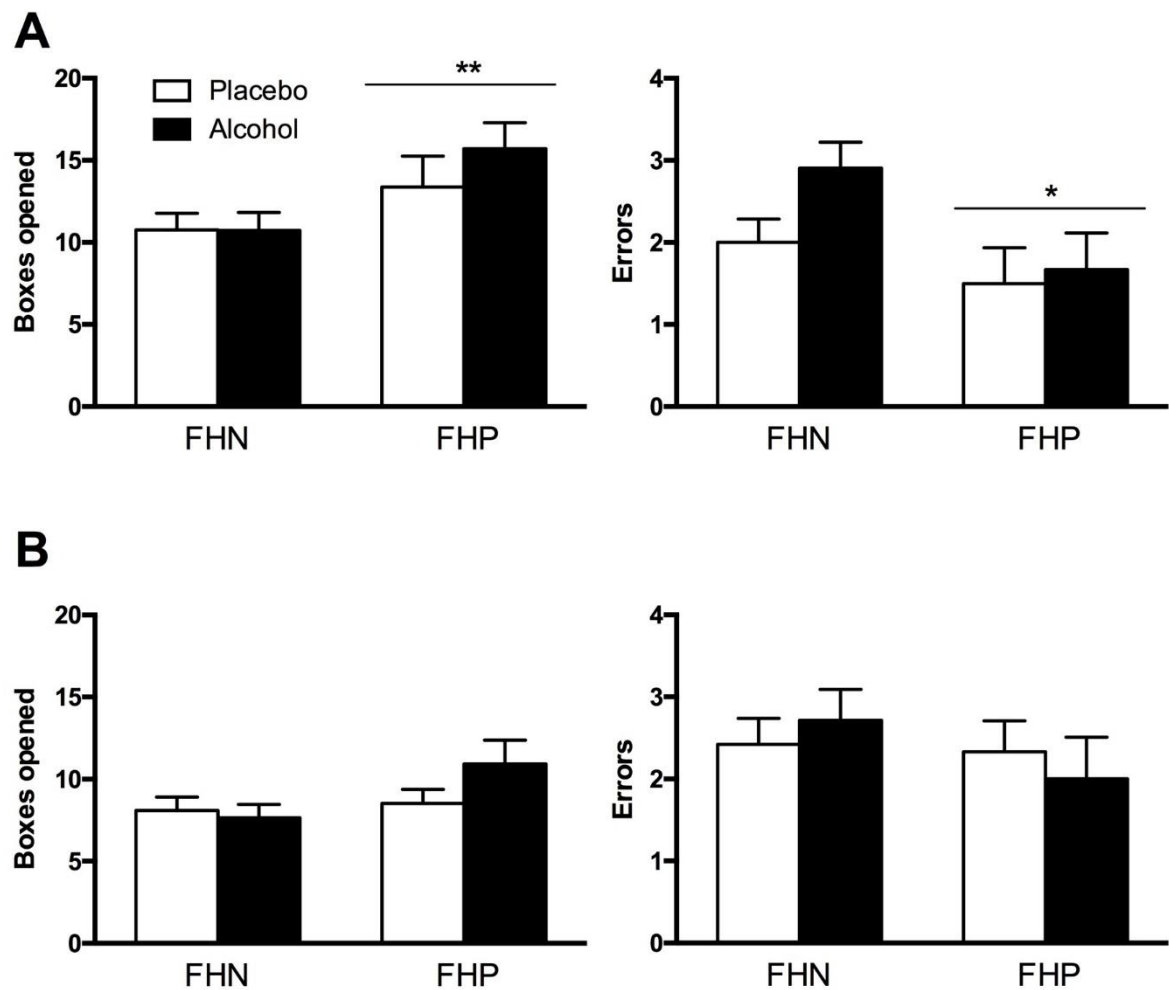
**Fig. 2.** Stop Signal Reaction Times (milliseconds; mean  $\pm$  SEM) on the Stop Signal task for placebo and acute alcohol, with matching FH positive and negative groups. Alcohol elevated SSRTi scores ( $p = .001$ ; a higher SSRT indicates greater motor impulsivity). (#)  $p = .059$ , #  $p < .05$  alcohol vs. placebo (same FH group).

**Fig. 3.** Information Sampling Task performance (mean  $\pm$  SEM): number of boxes opened (**A-C**) and errors (**B-D**). Alcohol did not disrupt performance on this task ( $ps > .05$ ). FHP subjects were more cautious than FHN: they opened more boxes ( $p = .011$ ) and made fewer errors ( $p = .021$ ) when the amount of win was fixed (**A-B**). When the challenge increased (decreased win for every box opened, **C-D**), all groups performed similarly. \*  $p < .05$  \*\*  $p < .01$  FHP vs. FHN.

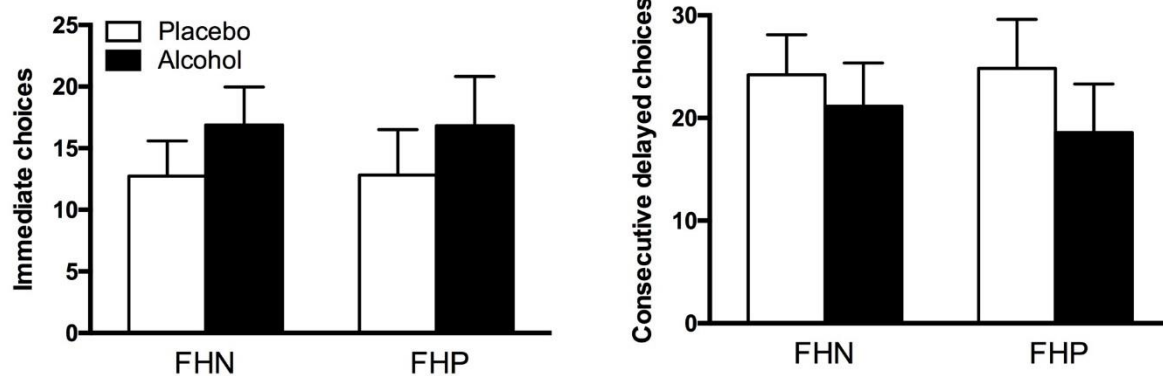
**Fig. 4.** Two choice Impulsivity paradigm performance: immediate choices and maximum number of consecutive delayed choices (mean  $\pm$  SEM). Although visual inspection of the graph suggests greater tendencies to choose risky (immediate) choices under the effects of acute alcohol, alcohol did not significantly disrupt performance on this task. FHP and FHN participants performed similarly ( $ps > .05$ ).

LIST OF FIGURES

Figure 1

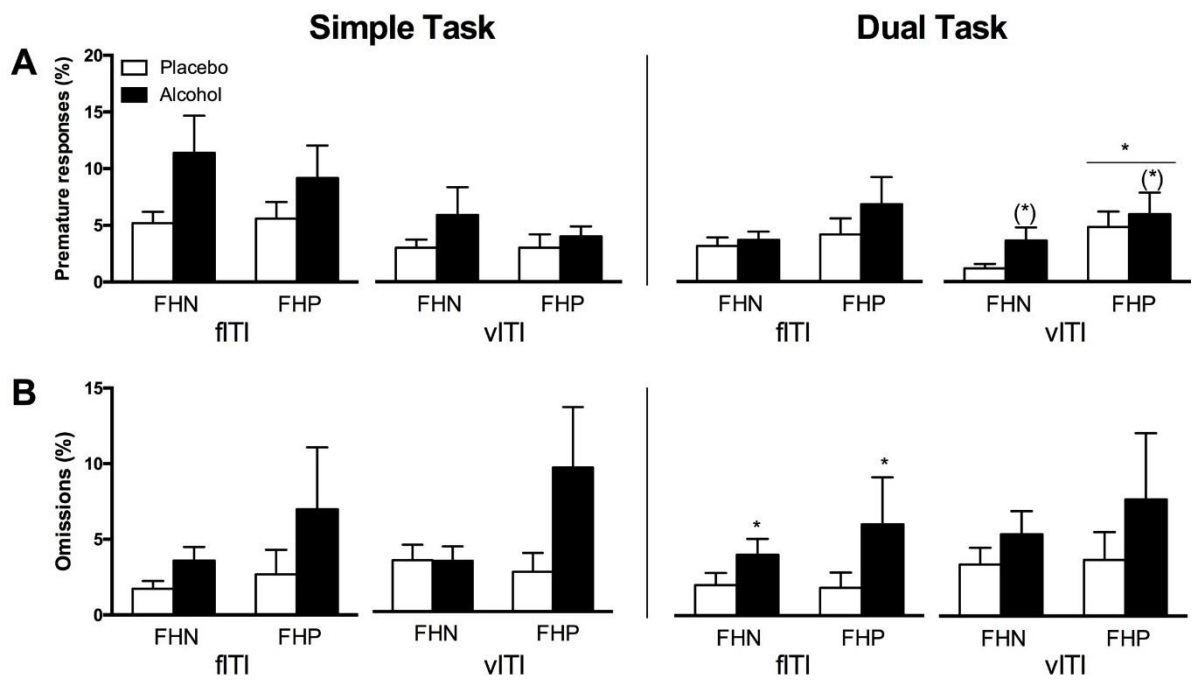


650 Figure 2



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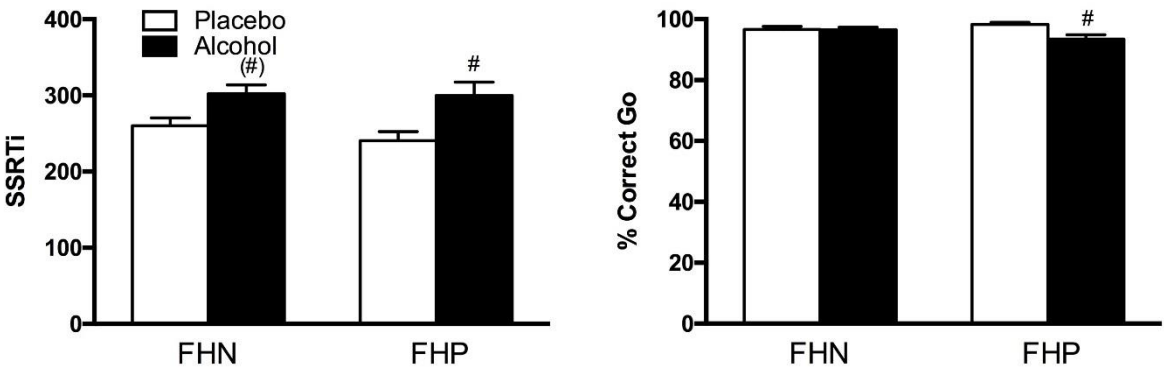
653 Figure 3



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Figure 4



662 **TABLE 1. Group characteristics (age, vocabulary, alcohol use, smoking) and trait measurements (self-reported impulsivity ratings) at baseline**  
663 **for placebo and alcohol dose (0.8 g/kg) groups**

	FHN		FHP		
	Placebo	Alcohol	Placebo	Alcohol	
<i>N</i>	19 (8m, 11f)	21 (10m, 11f)	12 (6m, 6f)	12 (6m, 6f)	
Age °	21.95 ± 3.22	21.714 ± 3.26	22.50 ± 3.50	22.00 ± 3.28	
Cigarette per day ( <i>N</i> )	1.42 ± 3.01 (5)	0.76 ± 2.07 (3)	0.33 ± 0.88 (2)	0.33 ± 0.88 (2)	
RAVLT °	9.42 ± 1.98	8.95 ± 1.56	9.33 ± 2.64	8.92 ± 1.83	
<i>Barratt Impulsivity Scale</i>					
Total Score	66.89 ± 11.02	59.67 ± 7.75 <sup>bb</sup>	66.08 ± 8.04	60.92 ± 9.05 <sup>bb</sup>	
Attentional subscale ¥	18.11 ± 3.54	15.57 ± 3.64 <sup>b</sup>	17.42 ± 3.85	16.67 ± 3.92 <sup>b</sup>	
Motor subscale	24.11 ± 4.67	22.48 ± 4.38 ( <sup>b</sup> )	24.50 ± 4.08	21.75 ± 3.67 ( <sup>b</sup> )	
Non-planning subscale	24.68 ± 5.27	21.61 ± 3.64 <sup>b</sup>	24.17 ± 4.01	22.5 ± 4.36 <sup>b</sup>	
<i>Alcohol Use Questionnaire</i>					
Units* of alcohol per week §	19.28 ± 7.99	20.03 ± 11.01	22.76 ± 14.94	20.17 ± 8.64	
Binge score §	26.74 ± 18.97	28.84 ± 24.14	22.50 ± 12.97	27.50 ± 15.94	
Alcohol Use score	46.02 ± 24.17	48.42 ± 30.97	45.26 ± 25.79	46.74 ± 16.86	
Alcohol Age onset	15.42 ± 1.89	16.14 ± 1.59	15.75 ± 1.48	14.50 ± 2.07 <sup>c</sup>	
AUDIT ¥	10.68 ± 5.25	9.14 ± 3.79	10.17 ± 4.37	10.00 ± 4.57	
<i>Drug Use Questionnaire (% , <i>N</i>) °</i>					
No drug use	47.40 (9)	66.70 (14)	41.70 (5)	33.30 (4)	
Occasional cannabis use	31.60 (6)	19.0 (4)	33.30 (4)	25.0 (3)	
Regular cannabis use	21.10 (4)	14.30 (3)	25.0 (3)	41.70 (5)	
BDI §	5.68 ± 6.07	5.05 ± 4.72	4.83 ± 4.49	7.41 ± 5.35	
BAC pre	0	1.04 ± 0.20	0	0.95 ± 0.40	
BAC post	0	0.91 ± 0.14	0	0.83 ± 0.19	

689 Abbreviations: ° non-parametric; RAVLT, Rey Auditory Verbal Learning Test; ¥ SQRT transformed; \* One alcohol unit = 8h of alcohol; § log<sub>10</sub> transformed;  
690 BDI, Beck Depression Inventory; BAC, breath alcohol concentration. (<sup>b</sup>) *p* = .06, <sup>b</sup> *p* < .05, <sup>bb</sup> *p* < .01, Alcohol effects; <sup>c</sup> *p* < .05, FH x Alcohol interaction. Values are  
691 expressed as mean ± SD.

**TABLE 2. Alcohol VAS ratings pre- and post- drink consumption for placebo and alcohol dose groups**

VAS	FHN					
	Placebo		Alcohol		Placebo	
	Pre	Post	Pre	Post	Pre	Post
Lightheaded <sup>***a a a</sup>	8.74 ± 3.72	15.95 ± 4.67	11.62 ± 3.97	23.67 ± 7.06	9.17±3.72	23.67±7.06
Relaxed <sup>b</sup>	66.63 ± 4.02	73.58 ± 3.85	55.47± 3.92	66.47±4.79	69.67±4.75	62.17±5.4
Contented <sup>*</sup>	59.47 ± 5.04	68.05 ± 4.81	53.95±4.21	63.28±4.55	66.33±5.06	60.67±5.4

\* p< .05, \*\*\* p< .001 time effect; <sup>aaa</sup> p< .001 time \* alcohol interaction; <sup>b</sup> p< .05 time \* FH interaction.  
 Values are expressed as mean ± SD.

698 **TABLE 3. Additional impulsivity measures for family history and alcohol groups.**

	FHN		FHP	
	Placebo	Alcohol	Placebo	Alcohol
<i>Time Estimation, N</i>	19 (8m, 11f)	21 (9m, 11f)	12 (6m, 6f)	12 (6m, 6f)
<i>Accuracy #</i>	85.65 ± 11.59	81.68 ± 13.48	84.06 ± 12.08	86.28 ± 11.59
<i>Stop Signal Task, N</i>	19 (8m, 10f)	21 (9m, 11f)	12 (6m, 6f)	12 (6m, 6f)
<i>Go Reaction time</i>	563.40 ± 112.66	575.39 ± 113.99	493.39 ± 116.81	552.74 ± 77.12
<i>Delay Discounting, N</i>	19 (8m, 11f)	21 (9m, 11f)	12 (6m, 6f)	12 (6m, 6f)
<i>k value §</i>	0.006 ± 0.12	0.041 ± 0.11 ( <sup>a</sup> )	0.004 ± 0.01	0.002 ± 0.01
<i>5CSRTT, N</i>	19 (8m, 11f)	21 (9m, 11f)	12 (6m, 6f)	12 (6m, 6f)
<i>Premature responses total</i>	6.53 ± 3.61	10.32 ± 9.68 ( <sup>b</sup> )	8.41 ± 7.40	12.50 ± 10.00
<i>Dual Task, N</i>	19 (8m, 11f)	21 (9m, 11f)	12 (6m, 6f)	12 (6m, 6f)
<i>Accuracy Responding fITI</i>	86.58 ± 3.52	80.25 ± 3.98 <sup>bbb</sup>	89.83 ± 4.12	71.33 ± 4.03
<i>Accuracy Responding vITI</i>	90.94 ± 2.11	73.95 ± 5.25 <sup>bbb</sup>	91.46 ± 3.73	68.08 ± 4.79

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700 Abbreviations: # arcsine transformed, § log<sub>10</sub> transformed. ( <sup>a</sup> ) *p*= .084, FH effects; ( <sup>b</sup> ) *p*=  
701 .058, <sup>b</sup> *p*< .05, <sup>bbb</sup> *p*< .001; ( <sup>c</sup> ) *p*= .088, FH x Alcohol interaction. Values are expressed as mean  
702 ± SEM.  
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